COMMENTS OF RADTECH INTERNATIONAL NORTH AMERICA

ON

VALIDATION OF GENETICALLY MODIFIED MOUSE MODELS

MARCH 10, 2004

My name is Martha Marrapese, and I am a partner with the law firm of Keller and Heckman LLP in Washington, DC. Our firm is a pioneer in the use of interdisciplinary approaches to problem-solving. Since 1971, we have had an in-house scientific staff that works closely with the firm's attorneys on matters of technical complexity. We currently have 16 staff scientists, most with Ph.D.'s in toxicology, organic, physical, and analytical chemistry, and polymer science. Many of our attorneys also have scientific backgrounds and government experience and expertise in multiple areas of the law.

I am here on behalf of RadTech International North America (RadTech). RadTech, a non-profit organization, is the association for the advancement of ultraviolet and electron beam (UV and EB) technology. This technology is in widespread use in terms of thousands of equipment installations worldwide and has been safely used for over three decades. RadTech serves as the industry forum for addressing the educational needs of the users and suppliers of UV and EB equipment and materials. RadTech's members represent companies, many of whom are small businesses, whose applications include adhesives, automotive parts, composites, packaging, flooring, graphic arts, electronics, plastics, and wood finishes.

UV and EB refer to a special way in which coatings, inks and adhesives on cans, wood and other products are cured or dried using a UV & EB process instead of conventional thermal curing. In effect, the ultraviolet light spectrum in a UV lamp and the focused electrons in EB curing interact with specially formulated chemistries to cure inks and coatings -- often more quickly and less costly than by other methods. A 2001 document issued by the U.S. Environmental Protection Agency (USEPA) Clean Air Technology Center entitled, Technical Bulletin on Ultraviolet and Electron Beam Cured Coatings, Inks and Adhesives,[1] provides a current and comprehensive analysis of UV/EB technology. Because of the resulting reduction in volatile organic content (VOC) emissions, less toxic materials, reduced waste and energy savings associated with the technology, UV/EB is generally regarded as an environmentally friendly technology.

I am here before you today because RadTech understands that plans are underway to move forward with standard, two-year skin cancer studies on two substances of interest in 2004, possibly starting as early as this spring.[2] The first of these substances, trimethylolpropane triacyrlate (TMPTA), can be a component of UV and EB curable coatings, inks, and adhesives in printing, wood furniture, metal, plastics, and automotive applications. Pentaerythritol triacrylate (PETA) is a low volume material that is sometimes used by the industry in similar applications.

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[1] *Technical Bulletin on Ultraviolet and Electron Beam Cured Coatings, Inks, and Adhesives*, U.S. EPA, Clean Air Technology Center, July, 2001, *available at* http://www.epa.gov/ttn/catc/dir1/fuv-eb.pdf.

[2] *See Toxicology Program Plans Research on Carcinogenicity of Two Triacrylates*, 26 Chem. Reg. Rep. (BNA), 1305-06 (Oct. 21, 2002).

More specifically, it is our understanding that the purpose of the two year studies on TMTPA and PETA is for validation purposes. NTP has stated that its reason for wanting to conduct the two year studies on TMPTA and PETA is to use the results to validate an experimental, short-term method of cancer detection that uses a strain of genetically altered ("transgenic") mice, Tg.AC mice, that are especially sensitive to skin injury.[3] RadTech would like to see this work brought in under ICCVAM's established internal peer-review procedures which require ICCVAM review of study protocols and validation design. We understand, however, that validation efforts associated with the mouse model used to evaluate TMPTA and PETA are not currently being undertaken through ICCVAM.

These proceedings are examining the role of two-year bioassays generally in validating shorter-term genetically modified mouse models. We want to raise some concerns with you that we think make the use of two-year bioassays a less than ideal method of validation in the TMPTA and PETA studies. Our primary concerns with respect to PETA and TMPTA are NTP's selection of the candidate test substances being used to validate the Tg.AC model and the dosages that have been selected.

With regard to the selection of the test substances, based on industry's experience with working with and testing acrylates, TMPTA and PETA are known to be moderate skin irritants and sensitizers. Skin and eye exposure are avoided in the workplace through the use of protective gloves and clothing. Consistent with principles of Responsible Care® and product

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3 http://ntp-server.niehs.nih.gov/Main_Pages/transgen/tg_summary.html.

stewardship, RadTech members are careful to instruct and visit customers to see that customers clearly understand how to handle UV and EB equipment and materials in the workplace. TMPTA and PETA were already evaluated in two-year skin cancer studies in mice in the 1980s and no skin cancer was observed for either substance.[4] These results are available in the peer-reviewed literature. Moreover, at doses that do not cause skin irritation, TMPTA and PETA did not generate a positive response even in the Tg.Ac mice. The researchers found a positive response in the genetically altered mice only at dose levels that irritate the skin.[5]

With respect to dose levels, our experts tell us that there is a generally recognized "rule of thumb", if you will, that scientific protocols *should* avoid dosing levels that are sufficient to cause irritation or an inflammatory response, because it is often difficult to establish whether an observed cell response stems from a truly "toxic" effect or whether the damage to the skin cells due to irritation causes the observed effect.[6] Last year, the Board of Scientific Counselors Technical Reports Review Subcommittee at NTP concluded that the relevance of the transgenic model in conjunction with PETA and TMPTA was unknown. It is our understanding that the effects of irritation at the high doses used in the assays was a factor in the Board's decision.

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[4] *See* Andrews LS, Clary JJ. Review of the toxicity of multifunctional acrylates. J. Toxicol. Environ. Health 1986; 19(2): 149-164. The possible relationship between irritant level doses and positive test results reported in this article for other acrylate compounds led industry to initiate long term bioassays on representative products in cooperation with the U.S. Environmental Protection Agency (EPA).

[5] *See* http://ntp-server.niehs.nih.gov/htdocs/liason/Sept2002Actions.html for the complete text of the withdrawal.

[6] *See* Tennant, R.W., Stasiewicz, S. Eastin, W.C., Mennear, J.H., and Spalding J. W. (2001). The Tg.AC (v -Ha-ras) transgenic mouse; Nature of the model. *Toxicol. Pathol.* **29** (Suppl.): 51-59. *See also* Spalding J.W., French, J.E., Tice, R.R., Furedi-Machacek, M., Haseman, J.K. and Tennant, R.W. (2000). Development of a transgenic mouse model for carcinogenesis bioassays: Evaluation of chemically induced skin tumors in Tg.AC mice. *Toxicol. Sci.* **49**: 241-254.

Our industry is in discussions with NTP concerning, in our view, the needs for non-irritating dose levels in the two-year study design for TMPTA and PETA, or at the very least, the need for carefully control and monitoring of irritation during the studies to obtain meaningful results. Thus far, NTP plans to proceed with standard two-year assays at the same irritating doses.

NTP's vision statement says in part that the agency would like "to move toxicology from a predominately observational science at the level of disease-specific models to a predominately predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations." In the case of TMPTA and PETA, the small business men and women members of RadTech believe that NTP has a two-fold responsibility: (1) to acknowledge how prior testing with irritating doses on transgenic mice likely leads to false positive outcomes; and (2) to use this information to avoid similar results in its planned studies.

As a class, acrylates as a class, are well-studied. Testing is currently underway in a cooperative program with USEPA to populate gaps that do exist in the environmental and occupational database for these substances. From an occupational safety and health standpoint, however, additional two-year studies on TMPTA and PETA contribute very little to this database. Given the discussion today, it is reasonable and prudent for NTP to consider whether to go forward with an investment of millions of taxpayer dollars to further study TMPTA and PETA, at least until there is a greater understanding of the issues raised in today's forum with

respect to the role of two year bioassays in the validation process for these genetic mouse models.

If NTP proceeds with these planned tests, then RadTech would like to see NTP acknowledge their limited purpose. RadTech requests that NTP recommend that the use of the data generated by these further studies be restricted to the purpose of validating the Tg.Ac model. There is already precedent for that course. In the case of the transgenic mouse data on TMPTA and PETA, NTP states that the results will "not be judged as an adequate study of the carcinogenic activity of TPMTA and PETA."[7] At the very least, we hope that NTP will consider adopting the same limited posture with respect to the role and utility of these long term studies.

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RadTech thanks you for the opportunity to present these comments. Please feel free to contact me at (202) 434-4123 or Gary Cohen, Executive Director of RadTech, at (240) 497-1242 if you have any questions, or if we can be of assistance in any way.

Sincerely yours,

Martha E. Marrapese

[7] *See* http://ntp-server.niehs.nih.gov/htdocs/liason/Sept2002Actions.html for the full text of the withdrawal.